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(54) Title: GRIP, HUMAN ADAPTER PROTEIN RELATED TO THE GRB2 FAMILY MEMBER

(57) Abstract

A polypeptide comprising the amino acid sequence shown in Figure 5 or any fragment thereof containing at least the amino acid residues encoded by nucleotide residues 151–459 or any polypeptide having substantially the same sequence and capable of binding to human CD28.

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SEQUENCE LISTING

<110> Glaxo Group Limited
Ellis, Jon H.

<120> Novel human adapter protein

<130> PU3535

<140>
<141>

<150> GB 9818124.1
<151> 1998-08-19

<160> 46

<170> PatentIn Ver. 2.1

<210> 1
<211> 152
<212> DNA
<213> Artificial Sequence

<220>
<221> CDS
<222> (5)..(133)

<220>
<223> Description of Artificial Sequence: Artificial gene encoding the CD28 cytoplasmic domain

<400> 1
catc gcg cgc agt aag agg agc agg ctc ctg cac agt gac tac atg aac 49
Ala Arg Ser Lys Arg Ser Arg Leu Leu His Ser Asp Tyr Met Asn
1 5 10 15

atg act cca cgt aga ccg ggt cca acg aga aag cat tac cag ccc tat 97
Met Thr Pro Arg Arg Pro Gly Pro Thr Arg Lys His Tyr Gln Pro Tyr
20 25 30

gca cca cct aga gac ttc gca gcc tat cgc tcc tga gcggccgcag 143
Ala Pro Pro Arg Asp Phe Ala Ala Tyr Arg Ser
35 40

cgcgcgatg 152

<210> 2
<211> 42
<212> PRT
<213> Artificial Sequence
<223> Description of Artificial Sequence: Artificial gene encoding the CD28 cytoplasmic domain

<400> 2
Ala Arg Ser Lys Arg Ser Arg Leu Leu His Ser Asp Tyr Met Asn Met
1 5 10 15

Thr Pro Arg Arg Pro Gly Pro Thr Arg Lys His Tyr Gln Pro Tyr Ala
20 25 30

Pro Pro Arg Asp Phe Ala Ala Tyr Arg Ser
35 40

<210> 3
<211> 152
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Artificial gene encoding the CD28 cytoplasmic domain

<400> 3

catcgcgcgc tgcggccgct caggagcgat aggctgcgaa gtctctaggt ggtgcatagg 60

gctggtaatg ctttctcgtt ggacccggtc tacgtggagt catgttcatg tagtcactgt 120

gcaggagcct gctcctctta ctgcgcgcga tg 152

<210> 4

<211> 993

<212> DNA

<213> Homo sapiens

<220>

<221> CDS

<222> (1)..(993)

<400> 4

atg gaa gct gtt gcc aag ttt gat ttc act gct tca ggt gag gat gaa 48

Met Glu Ala Val Ala Lys Phe Asp Phe Thr Ala Ser Gly Glu Asp Glu

1 5 10 15

ctg agc ttt cac act gga gat gtt ttg aag att tta agt aac caa gag 96

Leu Ser Phe His Thr Gly Asp Val Leu Lys Ile Leu Ser Asn Gln Glu

20 25 30

gag tgg ttt aag gcg gag ctt ggg agc cag gaa gga tat gtg ccc aag 144

Glu Trp Phe Lys Ala Glu Leu Gly Ser Gln Glu Gly Tyr Val Pro Lys

35 40 45

aat ttc ata gac atc cag ttt ccc aaa tgg ttt cac gaa ggc ctc tct 192

Asn Phe Ile Asp Ile Gln Phe Pro Lys Trp Phe His Glu Gly Leu Ser

50 55 60

cga cac cag gca gag aac tta ctc atg ggc aag gag gtt ggc ttc ttc 240

Arg His Gln Ala Glu Asn Leu Leu Met Gly Lys Glu Val Gly Phe Phe

65 70 75 80

atc atc cgg gcc agc cag agc tcc cca ggg gac ttc tcc atc tct gtc 288
Ile Ile Arg Ala Ser Gln Ser Ser Pro Gly Asp Phe Ser Ile Ser Val
85 90 95

agg cat gag gat gac gtt caa cac ttc aag gtc atg cga gac aac aag 336
Arg His Glu Asp Asp Val Gln His Phe Lys Val Met Arg Asp Asn Lys
100 105 110

ggt aat tac ttt ctg tgg act gag aag ttt cct tcc cta aat aag ctg 384
Gly Asn Tyr Phe Leu Trp Thr Glu Lys Phe Pro Ser Leu Asn Lys Leu
115 120 125

gta gac tac tac agg aca aat tcc atc tcc aga cag aag cag atc ttc 432
Val Asp Tyr Tyr Arg Thr Asn Ser Ile Ser Arg Gln Lys Gln Ile Phe
130 135 140

ctt aga gac aga acc cga gaa gac cag ggt cac cgg ggc aac agc ctg 480
Leu Arg Asp Arg Thr Arg Glu Asp Gln Gly His Arg Gly Asn Ser Leu
145 150 155 160

gac cgg agg tcc cag gga ggc cca cac ctc agt ggg gct gtg gga gaa 528
Asp Arg Arg Ser Gln Gly Gly Pro His Leu Ser Gly Ala Val Gly Glu
165 170 175

gaa atc cga cct tcg atg aac cgg aag ctg tcg gat cac ccc ccg acc 576
Glu Ile Arg Pro Ser Met Asn Arg Lys Leu Ser Asp His Pro Pro Thr
180 185 190

ctt ccc ctg cag cag cac cag cac cag cca cag cct ccg caa tat gcc 624
Leu Pro Leu Gln Gln His Gln His Gln Pro Gln Pro Pro Gln Tyr Ala
195 200 205

cca gcg ccc cag cag ctg cag cag ccc cca cag cag cga tat ctg cag 672
Pro Ala Pro Gln Gln Leu Gln Gln Pro Pro Gln Gln Arg Tyr Leu Gln
210 215 220

```
cac cac cat ttc cac cag gaa cgc cga gga ggc agc ctt gac ata aat   720
His His His Phe His Gln Glu Arg Arg Gly Gly Ser Leu Asp Ile Asn
225                 230                 235                 240

gat ggg cat tgt ggc acc ggc ttg ggc agt gaa atg aat gcg gcc ctc   768
Asp Gly His Cys Gly Thr Gly Leu Gly Ser Glu Met Asn Ala Ala Leu
                245                 250                 255

atg cat cgg aga cac aca gac cca gtg cag ctc cag gcg gca ggg cga   816
Met His Arg Arg His Thr Asp Pro Val Gln Leu Gln Ala Ala Gly Arg
            260                 265                 270

gtg cgg tgg gcc cgg gcg ctg tat gac ttt gag gcc ctg gag gat gac   864
Val Arg Trp Ala Arg Ala Leu Tyr Asp Phe Glu Ala Leu Glu Asp Asp
        275                 280                 285

gag ctg ggg ttc cac agc ggg gag gtg gtg gag gtc ctg gat agc tcc   912
Glu Leu Gly Phe His Ser Gly Glu Val Val Glu Val Leu Asp Ser Ser
    290                 295                 300

aac cca tcc tgg tgg acc ggc cgc ctg cac aac aag ctg ggc ttc ttc   960
Asn Pro Ser Trp Trp Thr Gly Arg Leu His Asn Lys Leu Gly Phe Phe
305                 310                 315                 320

cct gcc aac tac gtg gca ccc atg acc cga taa                       993
Pro Ala Asn Tyr Val Ala Pro Met Thr Arg
                325                 330
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<210> 5
<211> 330
<212> PRT
<213> Homo sapiens

<400> 5

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Met Glu Ala Val Ala Lys Phe Asp Phe Thr Ala Ser Gly Glu Asp Glu
  1               5                  10                  15
```

Leu Ser Phe His Thr Gly Asp Val Leu Lys Ile Leu Ser Asn Gln Glu
20 25 30

Glu Trp Phe Lys Ala Glu Leu Gly Ser Gln Glu Gly Tyr Val Pro Lys
35 40 45

Asn Phe Ile Asp Ile Gln Phe Pro Lys Trp Phe His Glu Gly Leu Ser
50 55 60

Arg His Gln Ala Glu Asn Leu Leu Met Gly Lys Glu Val Gly Phe Phe
65 70 75 80

Ile Ile Arg Ala Ser Gln Ser Ser Pro Gly Asp Phe Ser Ile Ser Val
85 90 95

Arg His Glu Asp Asp Val Gln His Phe Lys Val Met Arg Asp Asn Lys
100 105 110

Gly Asn Tyr Phe Leu Trp Thr Glu Lys Phe Pro Ser Leu Asn Lys Leu
115 120 125

Val Asp Tyr Tyr Arg Thr Asn Ser Ile Ser Arg Gln Lys Gln Ile Phe
130 135 140

Leu Arg Asp Arg Thr Arg Glu Asp Gln Gly His Arg Gly Asn Ser Leu
145 150 155 160

Asp Arg Arg Ser Gln Gly Gly Pro His Leu Ser Gly Ala Val Gly Glu
165 170 175

Glu Ile Arg Pro Ser Met Asn Arg Lys Leu Ser Asp His Pro Pro Thr
180 185 190

Leu Pro Leu Gln Gln His Gln His Gln Pro Gln Pro Pro Gln Tyr Ala
195 200 205

Pro Ala Pro Gln Gln Leu Gln Gln Pro Pro Gln Gln Arg Tyr Leu Gln
210 215 220

His His His Phe His Gln Glu Arg Arg Gly Gly Ser Leu Asp Ile Asn
225 230 235 240

Asp Gly His Cys Gly Thr Gly Leu Gly Ser Glu Met Asn Ala Ala Leu
245 250 255

Met His Arg Arg His Thr Asp Pro Val Gln Leu Gln Ala Ala Gly Arg
260 265 270

Val Arg Trp Ala Arg Ala Leu Tyr Asp Phe Glu Ala Leu Glu Asp Asp
275 280 285

Glu Leu Gly Phe His Ser Gly Glu Val Val Glu Val Leu Asp Ser Ser
290 295 300

Asn Pro Ser Trp Trp Thr Gly Arg Leu His Asn Lys Leu Gly Phe Phe
305 310 315 320

Pro Ala Asn Tyr Val Ala Pro Met Thr Arg
325 330

<210> 6
<211> 993
<212> DNA
<213> Homo sapiens

<400> 6
ttatcgggtc atgggtgcca cgtagttggc agggaagaag cccagcttgt tgtgcaggcg 60
gccggtccac caggatgggt tggagctatc caggacctcc accacctccc cgctgtggaa 120
ccccagctcg tcatcctcca gggcctcaaa gtcatacagc gcccgggccc accgcactcg 180
ccctgccgcc tggagctgca ctgggtctgt gtgtctccga tgcatgaggg ccgcattcat 240
ttcactgccc aagccggtgc cacaatgccc atcatttatg tcaaggctgc ctcctcggcg 300
ttcctggtgg aaatggtggt gctgcagata tcgctgctgt gggggctgct gcagctgctg 360
gggcgctggg gcatattgcg gaggctgtgg ctggtgctgg tgctgctgca ggggaagggt 420
cgggggggtga tccgacagct tccggttcat cgaaggtcgg atttcttctc ccacagcccc 480
actgaggtgt gggcctccct gggacctccg gtccaggctg ttgccccggt gaccctggtc 540

ttctcgggtt ctgtctctaa ggaagatctg cttctgtctg gagatggaat ttgtcctgta 600
gtagtctacc agcttattta gggaaggaaa cttctcagtc cacagaaagt aattaccctt 660
gttgtctcgc atgaccttga agtgttgaac gtcatcctca tgcctgacag agatggagaa 720
gtcccctggg gagctctggc tggcccggat gatgaagaag ccaacctcct tgcccatgag 780
taagttctct gcctggtgtc gagagaggcc ttcgtgaaac catttgggaa actggatgtc 840
tatgaaattc ttgggcacat atccttcctg gctcccaagc tccgccttaa accactcctc 900
ttggttactt aaaatcttca aaacatctcc agtgtgaaag ctcagttcat cctcacctga 960
agcagtgaaa tcaaacttgg caacagcttc cat 993

<210> 7
<211> 240
<212> DNA
<213> Artificial Sequence

<220>
<221> CDS
<222> (9)..(239)

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 7
agcttacc atg ggg ggt tct cat cat cat cat cat cat ggt atg gct agc 50
Met Gly Gly Ser His His His His His His Gly Met Ala Ser
1 5 10

atg act ggt gga cag caa atg ggt cgg gat ctg tac gac gat gac gat 98
Met Thr Gly Gly Gln Gln Met Gly Arg Asp Leu Tyr Asp Asp Asp Asp
15 20 25 30

aag tct aga gga tcc aag ctt atg gaa gct gtt gcc aag ttt gat ttc 146
Lys Ser Arg Gly Ser Lys Leu Met Glu Ala Val Ala Lys Phe Asp Phe
35 40 45

act gct tca ggt gag gat gaa ctg agc ttt cac act gga gat gtt ttg 194
Thr Ala Ser Gly Glu Asp Glu Leu Ser Phe His Thr Gly Asp Val Leu
50 55 60

aag att tta agt aac caa gag gag tgg ttt aag gcg gag ctt ggg a 240
Lys Ile Leu Ser Asn Gln Glu Glu Trp Phe Lys Ala Glu Leu Gly
65 70 75

<210> 8
<211> 77
<212> PRT
<213> Artificial Sequence
<223> Description of Artificial Sequence: Synthetic construct

<400> 8
Met Gly Gly Ser His His His His His His Gly Met Ala Ser Met Thr
1 5 10 15

Gly Gly Gln Gln Met Gly Arg Asp Leu Tyr Asp Asp Asp Asp Lys Ser
20 25 30

Arg Gly Ser Lys Leu Met Glu Ala Val Ala Lys Phe Asp Phe Thr Ala
35 40 45

Ser Gly Glu Asp Glu Leu Ser Phe His Thr Gly Asp Val Leu Lys Ile
50 55 60

Leu Ser Asn Gln Glu Glu Trp Phe Lys Ala Glu Leu Gly
65 70 75

<210> 9
<211> 240
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 9
tcccaagctc cgccttaaac cactcctctt ggttacttaa aatcttcaaa acatctccag 60
tgtgaaagct cagttcatcc tcacctgaag cagtgaaatc aaacttggca acagcttcca 120
taagcttgga tcctctagac ttatcgtcat cgtcgtacag atcccgaccc atttgctgtc 180
caccagtcat gctagccata ccatgatgat gatgatgatg agaaccccc atggtaagct 240

<210> 10
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<221> SITE
<222> (1)
<223> lysyl residue bearing a biotin moiety

<220>
<223> Description of Artificial Sequence: Synthesised peptide

<400> 10
Lys Leu Leu His Ser Asp Tyr Met Asn Met Thr Pro Arg
1 5 10

<210> 11
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<221> SITE
<222> (1)
<223> lysyl residue bearing a biotin moiety

<220>
<221> MOD_RES
<222> (7)
<223> PHOSPHORYLATION

<220>
<223> Description of Artificial Sequence: Synthesised peptide

<400> 11
Lys Leu Leu His Ser Asp Tyr Met Asn Met Thr
1 5 10

<210> 12
<211> 81
<212> DNA
<213> Artificial Sequence

<220>
<221> CDS
<222> (1)..(81)

<220>
<223> Description of Artificial Sequence: Polylinker

<400> 12

gct agg tcg acg gcc atg gta tcg atg aat tcc tgc agc ccg gcg cgc 48
Ala Arg Ser Thr Ala Met Val Ser Met Asn Ser Cys Ser Pro Ala Arg
1 5 10 15

tct gga tct act agt gcg gcc gcc acc gcg gtg 81
Ser Gly Ser Thr Ser Ala Ala Ala Thr Ala Val
20 25

<210> 13
<211> 27
<212> PRT
<213> Artificial Sequence
<223> Description of Artificial Sequence: Polylinker

<400> 13
Ala Arg Ser Thr Ala Met Val Ser Met Asn Ser Cys Ser Pro Ala Arg
1 5 10 15

Ser Gly Ser Thr Ser Ala Ala Ala Thr Ala Val
20 25

<210> 14
<211> 57
<212> DNA
<213> Artificial Sequence

<220>
<221> CDS
<222> (1)..(57)

<220>
<223> Description of Artificial Sequence: Polylinker

<400> 14

cat atg gcc atg gag gcc ccg gcg cgc tct gga tcc gtc gac ctg cag 48
His Met Ala Met Glu Ala Pro Ala Arg Ser Gly Ser Val Asp Leu Gln
1 5 10 15

cca agc taa 57
Pro Ser

<210> 15
<211> 18
<212> PRT
<213> Artificial Sequence
<223> Description of Artificial Sequence: Polylinker

<400> 15
His Met Ala Met Glu Ala Pro Ala Arg Ser Gly Ser Val Asp Leu Gln
1 5 10 15

Pro Ser

<210> 16
<211> 63
<212> DNA
<213> Artificial Sequence

<220>
<221> CDS
<222> (1)..(63)

<220>
<223> Description of Artificial Sequence: Polylinker

<400> 16
cat atg gcc atg gag gcc ccg ggg atc gga tcc gat ccg aat tcg agc 48
His Met Ala Met Glu Ala Pro Gly Ile Gly Ser Asp Pro Asn Ser Ser
1 5 10 15

tcg aga gat cta tga 63
Ser Arg Asp Leu
20

<210> 17
<211> 20
<212> PRT
<213> Artificial Sequence
<223> Description of Artificial Sequence: Polylinker

<400> 17
His Met Ala Met Glu Ala Pro Gly Ile Gly Ser Asp Pro Asn Ser Ser
1 5 10 15

Ser Arg Asp Leu
20

<210> 18
<211> 42
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Primer

<400> 18
agggaattcc tcgagtcatt ggggagtttc tgcattttct ag 42

<210> 19
<211> 38
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Primer

<400> 19
catcgcgcgc agtaagagga gcaggctcct gcacagtg 38

<210> 20
<211> 58
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Primer

<400> 20
tctcgttgga cccggtctac gtggagtcat gttcatgtag tcactgtgca ggagcctg 58

<210> 21
<211> 56
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Primer

<400> 21
ccgggtccaa cgagaaagca ttaccagccc tatgcaccac ctagagactt cgcagc 56

<210> 22
<211> 49
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Primer

<400> 22
catcgcgcgc tgcggccgct caggagcgat aggctgcgaa gtctctagg 49

<210> 23
<211> 58
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Primer

<400> 23
tctcgttgga cccggtctac gtggagtcat gttcatgaag tcactgtgca ggagcctg 58

<210> 24
<211> 58
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Primer

<400> 24
tctcgttgga cccgctctac gtgcagtcat gttcatgtag tcactgtgca ggagcctg 58

<210> 25
<211> 56
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Primer

<400> 25
gcgggtccaa cgagaaagca ttaccaggcc tatgcagcac ctagagactt cgcagc 56

<210> 26
<211> 29
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Primer

<400> 26
catcggatcc gaagatttgc cccatcatg 29

<210> 27
<211> 28
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Primer

<400> 27
catcgaattc tcatcgcctc tgctgtgc 28

<210> 28
<211> 34
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Primer

<400> 28
catcgcgcgc agtaagagga gcaggctcct gcac 34

<210> 29
<211> 62
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Primer

<400> 29
tctcgttgga cccggtctac gtggagtcat gttcacgtag tcactgtgca ggagcctgct 60
cc 62

<210> 30
<211> 62
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Primer

<400> 30
tctcgttgga cccggtctac gtggagtcat tttcatgtag tcactgtgca ggagcctgct 60
cc 62

<210> 31
<211> 62
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Primer

<400> 31
tctcgttgga cccggtctac gtggagtcat tttcacgtag tcactgtgca ggagcctgct 60
cc 62

<210> 32
<211> 49
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Primer

<400> 32
catcgcgcgc ggatccaagc ttatggaagc tgttgccaag tttgatttc 49

<210> 33
<211> 48
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Primer

<400> 33
catcgaattc gtcgacgcgg ccgcttatcg ggtcatgggt gccacgta 48

<210> 34
<211> 34
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Primer

<400> 34
catcggatcc atagacatcc agtttcccaa atgg 34

<210> 35
<211> 34
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Primer

<400> 35
catcgaattc ttactggtct tctcgggttc tgtc 34

<210> 36
<211> 34
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Primer

<400> 36
catcggatcc ttccttagag acagaacccg agaa 34

<210> 37
<211> 37
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Primer

<400> 37
catcgaattc ttaccaccgc actcgccctg ccgcctg 37

<210> 38
<211> 48
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Primer

<400> 38
catcgcggcc gcgtcgacga attcttatcg ggtcatgggt gccacgta 48

<210> 39
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Primer

<400> 39
accacagtcc atgccatcac 20

<210> 40
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Primer

<400> 40
tccaccaccc tgttgctgta 20

<210> 41
<211> 31
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Primer

<400> 41
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<210> 42
<211> 31
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Primer

<400> 42
gatcctctag acttatcgtc atcgtcgtac a 31

<210> 43
<211> 47
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Primer

<400> 43
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<210> 44
<211> 28
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Primer

<400> 44
gatggaattc ttatcgggtc atgggtgc 28

<210> 45
<211> 77
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Primer

<400> 45
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agctgttgcc aagtttg 77

<210> 46
<211> 41
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Primer

<400> 46
ataagatggc gcgcggatcc ttacataaac taagtgaaga g 41

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 99/02738

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12N15/12 C07K14/47 A61K38/17 C12Q1/68

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C12N C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE EMBL NUCLEOTIDE DATABASE, [Online] EBI, Hinxton, GB Trembl, ID 04376, 1 June 1998 (1998-06-01) BURGESS, J. ET AL.: "Growth factor receptor bound-protein 21ike" retrieved from TREMBL Database accession no. 043726 XP002119673 abstract --- WO 98 40482 A (INCYTE PHARMA INC ;BANDMAN OLGA (US); DIEGIDIO ANTHONY P (US)) 17 September 1998 (1998-09-17) claims 1-18 --- -/--	1-5,13 1-13

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 October 1999	11. 11. 99

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Nauche, S

4

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	QIU M, HUA S, AGRAWAL M, LI G, CAI J, CHAN E, ZHOU H, LUO Y, LIU M: "Molecular cloning and expression of human grap-2, a novel leukocyte-specific SH2- and SH3-containing" BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, vol. 253, no. 2, 18 December 1998 (1998-12-18), pages 443-447, XP002119672 ORLANDO, FL US the whole document	1-5,13

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 99/02738

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claims 10-12 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/GB 99/02738

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9840482 A	17-09-1998	US 5874224 A	23-02-1999
		AU 6692598 A	29-09-1998
		EP 0968286 A	05-01-2000